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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/173,463	10/14/1998	MARGARET E. BLACK	240052.429	1873
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EXAMINER				
FRONDA, CHRISTIAN L				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/173,463

Applicant(s)

BLACK, MARGARET E.

Examiner

CHRISTIAN L. FRONDA

Art Unit

1652

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 7-61 is/are pending in the application.
- 4a) Of the above claim(s) 16-60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-15 and 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 October 1998 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/C)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/14/2008 has been entered.
2. Claims 1-5 and 7-61 are pending in the instant application. Claims 16-60 have previously been withdrawn from consideration as drawn to a non-elected invention.
3. Claims 1-5, 7-15, and 61 are under consideration in this Office Action. The previous rejections have been withdrawn. New rejections and new grounds of rejection are presented in the instant Office Action in view of the amendments to the claims filed 07/14/2008.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 1-5, 7-15, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 2, the recitation of the nucleotide sequences of SEQ ID NOs: 1 and 116-121 do not particularly identify the specific amino acid residues in the DRH nucleoside binding site and Q substrate binding domain of the *Herpesviridae* thymidine kinase which are to be mutated. Amending the claims to recite the specific amino acid sequence of the *Herpesviridae* thymidine kinase to be mutated or reciting that the binding domain is encoded by the SEQ ID

NOs may help in overcoming the rejection. Dependent claims 2-5 and 7-15 are also rejected because they do not correct the defect of claim 1 or claim 2.

In claim 61, the phrase “nucleic acid molecule encoding a *Herpesviridae* thymidine kinase enzyme of SEQ ID NO: 1” renders the claim vague and indefinite since SEQ ID NO: 1 is disclosed as a nucleotide sequence and not an amino acid sequence. Amending the claim to recite that the nucleic acid molecule comprises SEQ ID NO: 1 and encodes a *Herpesviridae* thymidine kinase may aid in overcoming the rejection.

In claims 14 and 15, the recitation of the tissue-specific promoter is vague and indefinite because this limitation lacks antecedent basis in claim 13. It appear that claims 14 and 15 should depend from claim 12. Appropriate correction is requested.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5, 7-15, and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed toward the current USPTO Written Description Training Materials made available to the public on 04/11/2008 for information regarding examination of patent claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph.

The claims are genus claims encompassing a genus of isolated nucleic acid molecules encoding *Herpesviridae* thymidine kinase enzymes comprising at least one mutation in the Q

substrate binding domain encoded by nucleotides selected from the group consisting of any of SEQ ID NOs: 116-121, a genus of isolated nucleic acid molecules encoding *Herpesviridae* thymidine kinase enzymes comprising at least three of the recited mutations toward the N-terminus and C-terminus of a DRH nucleoside binding site, a genus of isolated nucleic acid molecules encoding *Herpesviridae* thymidine kinase enzymes comprising SEQ ID NO: 107 or SEQ ID NO: 108 wherein said SEQ ID NO: 107 or SEQ ID NO: 108 comprises amino acid substitutions for wild type amino acids at positions 159-161 and 168-169. The scope of each genus includes many members with widely differing amino acid and/or nucleotide sequences and structures, where each genus is highly variable because a significant number of structural and biological differences between genus members exists.

The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; reference of record) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships. The reference of Sen et al. (Appl Biochem Biotechnol. 2007 Dec;143(3):212-23) teaches *in vitro* recombination techniques such as DNA shuffling, staggered extension process (StEP), random chimeragenesis on transient templates (RACHITT), iterative truncation for the creation of hybrid enzymes (ITCHY), recombined extension on truncated templates (RETT), and so on have been developed to mimic and accelerate nature's recombination strategy. However, such directed evolution techniques only describes methods for searching and screening for enzymes with a desired property or properties.

The recitation of the *Herpesviridae* thymidine kinase enzyme comprising at least one mutation in the Q substrate binding domain encoded by nucleotides selected from the group consisting of any of SEQ ID NOs: 116-121, the *Herpesviridae* thymidine kinase enzymes comprising at least three of the recited mutations toward the N-terminus and C-terminus of a DRH nucleoside binding site, and the *Herpesviridae* thymidine kinase enzymes comprising SEQ ID NO: 107 or SEQ ID NO: 108 wherein said SEQ ID NO: 107 or SEQ ID NO: 108 comprises amino acid substitutions for wild type amino acids at positions 159-161 and 168-169 represents a partial structure.

The specification discloses general guidance for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucleotides having mutant codons at amino acid residues 112-132 (Q substrate binding domain) of the encoded *Herpesviridae* thymidine kinase (see Example 10, pages 73-74 of substitute specification filed 07/14/2008). The specification states that mutants were assayed for ability to phosphorylate thymidine, acyclovir, and ganciclovir (see p. 74, lines 29-34).

The specification, however, does not describe and define any structural features, nucleotide and amino acid sequences, and/or biological functions that are commonly possessed by members of each genus. The specification does not provide a correlation between any structure and an altered substrate specificity activity based on which those of ordinary skill in the art could predict which amino acids can vary from the amino acid sequence encoded by SEQ ID NO: 1 without losing thymidine kinase activity. Further, there is no art-recognized correlation between any structure and an altered substrate specificity activity based on which those of ordinary skill in the art could predict which amino acids can vary from the amino acid sequence encoded by SEQ ID NO: 1 without losing thymidine kinase activity. Consequently, there is no information about which amino acids can vary from and still retain the catalytic activity.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose additional nucleic acid molecules as encompassed by the claims. As such the disclosure of the above mentioned guidance for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucleotides having mutant codons at amino acid residues 112-132 (Q substrate binding domain) of the encoded *Herpesviridae* thymidine kinase is insufficient to be representative of the attributes and features common to all the members of each claimed genus.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at

page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of each claimed genus.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

According to MPEP 2143:

“Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel."

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5, 7-15, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loeb et al. (WO95030007-A1, published 11/09/1995; and Accession AAT05183, 14-June-1996; PTO 892) or Accession J03366 (20-FEB-1989; PTO 892) in view of the combined teachings of Black et al. (J Gen Virol. 1996 Jul;77 (Pt 7):1521-7; PTO 892), Balasubramaniam et al. (J Gen Virol. 1990 Dec;71 (Pt 12):2979-87; reference of record), Brown et al. (Nat Struct Biol. 1995 Oct;2(10):876-81; reference of record), and Deonarian et al. (Gene Ther. 1995 Jun;2(4):235-44; reference of record).

Loeb et al. teach an isolated nucleic acid molecule (Accession AAT05183) that is 100% identical to SEQ ID NO: 1 of the instant application and encodes a *Herpesviridae* thymidine kinase, and comprises a nucleotide sequence of SEQ ID NOS: 116-118 (see alignment of SEQ ID NOS: 1 and 116-118 to Accession AAT05183).

Loeb et al (WO95030007-A1) teach that the said *Herpesviridae* thymidine kinase encoded by the said isolated nucleic acid molecule (Accession AAT05183) comprises the DRH nucleoside binding site. Loeb et al teach site-directed mutagenesis techniques to make truncated thymidine kinase mutants and alter specific amino acid residues in its amino acid sequence. Loeb et al teach isolated nucleic acid molecules encoding mutant *Herpesviridae* thymidine kinases comprising mutations downstream from a DRH nucleoside binding site which increases

its biological activity as compared to an unmutated thymidine kinase; and that such mutants are capable of phosphorylating nucleoside analogs such as ganciclovir and acyclovir at least one-fold over a wild-type thymidine kinase. Loeb et al teach vectors comprising said isolated nucleic acid molecules encoding mutant *Herpesviridae* thymidine kinases and promoters including MoMLV LTR and tyrosine hydroxylase promoter. See entire publication especially Examples 1-9 and claims 1-37.

Accession J03366 teaches an isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 119 and encoding a Herpes simplex virus type 1 thymidine kinase (see alignment of SEQ ID NO: 119 to Accession J03366).

The teachings of Loeb et al. and Accession J03366 differ from the claims in that the isolated nucleic acid molecule does not encode a *Herpesviridae* thymidine kinase comprising the recited mutation in the Q substrate binding domain.

Black et al. teach site directed mutagenesis techniques to alter specific amino acid residues in herpes simplex virus thymidine kinase (see entire publication, especially pages 1522-1526).

Balasubramaniam et al. teach a multiple alignment of the amino acid sequences of 12 herpesviral deoxythymidine kinases which shows that a conserved glutamine (Q) residue at position 127 (see entire publication and Fig. 1). Balasubramaniam et al. further teach that the most conserved site in the herpesviral deoxythymidine kinases consists of the DRH motif which is involved in thymine recognition (see (iii) *Sites 3 and 4*, p. 2981).

Brown et al. teach that the region consisting of residues 161-192, which contains both the conserved glutamine residue at position 127 and the DRH motif taught by Balasubramaniam et al., is implicated in nucleoside binding (see **Nucleoside binding**, p. 878-879).

Deonarian et al. teaches and reviews the methods for the genetic delivery of enzymes such as thymidine kinase for cancer therapy (see entire publication).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the isolated nucleic acid of Loeb et al. (Accession AAT05183) or of Accession J03366 using the site-directed mutagenesis techniques of Loeb et al. and Black et al. to make mutations in the Q substrate binding domain or make truncated thymidine kinase mutants as recited to create an isolated nucleic acid encoding a mutant thymidine kinase with altered the substrate specificity. It would have been obvious to one of ordinary skill in the art to insert the modified isolated nucleic acid molecule in the vectors of Loeb et al. which can be transformed into host cells for the recombinant production of the mutant thymidine kinase with altered the substrate specificity.

One of ordinary skill in the art at the time the invention was made would be motivated to do this because Balasubramaniam et al. and Brown et al. teach that the Q substrate binding domain and the DRH binding domain are important in nucleoside binding and that in order to obtain mutants having the desired properties (i.e. increased enzyme activity or greater substrate/analog/prodrug specificity) this region must be modified. Furthermore, thymidine kinase mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Deonarian et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because site-directed mutagenesis techniques are well known and developed in the art as evidenced by the teachings of Black et al.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thornton*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-5, 7-15, and 61 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 5,877,010 in view of the combined teachings of Black et al. (J Gen Virol. 1996 Jul;77 (Pt 7):1521-7; PTO 892), Balasubramaniam et al. (J Gen Virol. 1990 Dec;71 (Pt 12):2979-87; reference of record), Brown et al. (Nat Struct Biol. 1995 Oct;2(10):876-81; reference of record), and Deonarian et al. (Gene Ther. 1995 Jun;2(4):235-44; reference of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons stated below.

U.S. Patent No. 5,877,010 ('010 patent) teaches to SEQ ID NO: 1 of the instant application which encodes a *Herpesviridae* thymidine kinase, and comprises a nucleotide sequence of SEQ ID NOs: 116-118. The '010 patent teaches that the said *Herpesviridae* thymidine kinase encoded by the said SEQ ID NO: 1 comprises the DRH nucleoside binding site. The '010 patent teach site-directed mutagenesis techniques to make truncated thymidine kinase mutants and alter specific amino acid residues in its amino acid sequence. The '010 patent teach isolated nucleic acid molecules encoding mutant *Herpesviridae* thymidine kinases comprising mutations downstream from a DRH nucleoside binding site which increases its biological activity as compared to an unmutated thymidine kinase; and that such mutants are capable of phosphorylating nucleoside analogs such as ganciclovir and acyclovir at least one-fold over a wild-type thymidine kinase. The '010 patent teach vectors comprising said isolated nucleic acid molecules encoding mutant *Herpesviridae* thymidine kinases and promoters including MoMLV LTR and tyrosine hydroxylase promoter.

The claims and teachings of the '010 patent differ from the claims of the instant application in that the isolated nucleic acid molecule does not encode a *Herpesviridae* thymidine kinase comprising the recited mutation in the Q substrate binding domain.

The teachings of Black et al., Balasubramaniam et al., Brown et al., and Deonarian et al. have been stated above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify SEQ ID NO: 1 of the '010 patent using the site-directed mutagenesis techniques of Black et al. to make mutations in the Q substrate binding domain or make truncated thymidine kinase mutants as recited to create an isolated nucleic acid encoding a mutant thymidine kinase with altered the substrate specificity. It would have been obvious to one of ordinary skill in the art to insert the modified isolated nucleic acid molecule in the vectors of the '010 patent which can be transformed into host cells for the recombinant production of the mutant thymidine kinase with altered the substrate specificity.

One of ordinary skill in the art at the time the invention was made would be motivated to do this because Balasubramaniam et al. and Brown et al. teach that the Q substrate binding domain and the DRH binding domain are important in nucleoside binding and that in order to obtain mutants having the desired properties (i.e. increased enzyme activity or greater substrate/analog/prodrug specificity) this region must be modified. Furthermore, thymidine kinase mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Deonarian et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because site-directed mutagenesis techniques are well known and developed in the art as evidenced by the teachings of Black et al.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on (571)272-0934. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian L. Fronda/

Primary Examiner

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